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A review of global health technology assessments of non-VKA oral anticoagulants in non-valvular atrial fibrillation

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ABSTRACT

Background: This review assessed global health technology assessment (HTA) reports and recommendations of non-vitamin K oral anticoagulants (NOACs) in non-valvular atrial fibrillation (NVAF).
Methods: NHTA agency websites were searched for HTA reports evaluating NOACs versus NOACs or vitamin K antagonists. HTA methods and information on patient involvement/access were collected and empirically analyzed.
Results: The review identified 38 unique HTA reports published between 2012 and 2017 in 16 countries including 11 in Europe. NOACs that were cost-effective per local willingness-to-pay (WTP) thresholds were positively recommended for the treatment of NVAF. WTP thresholds ranged from €20,000 to 69,000. Apixaban was recommended in 10/12 (83%) countries, dabigatran in 9/13 (69%) countries, and rivaroxaban in 10/13 (76%) over warfarin. Edoxaban was recommended in 5/7 (71%) countries. Economic evaluations and recommendations comparing NOACs were sparse (two or three countries per NOAC) and generally favored apixaban and edoxaban, followed by dabigatran. Eleven HTA reports from four countries considered the patient voice (Canada [n = 3], Scotland [n = 3], England [n = 4], Brazil [n = 1]); however, only 2/11 (18%) developed recommendations based on this. Among the reports with a positive recommendation, 26/30 (87%) featured a decision that aligned with the approved regulatory label.
Conclusions: Most agencies recommended NOACs over warfarin for patients with NVAF. Few countries made statements recommending one NOAC over another. Given different WTP thresholds, a drug that is cost-effective in one market may not be in another. Therefore, the various NOAC recommendations from HTA agencies cannot be generalized across different countries.

Abbreviations: AF, atrial fibrillation; BIM, budget impact model; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; CMA, cost-minimization analysis; CUA, cost-utility analysis; HAQI, Healthcare Access and Quality Index; HTA, health technology assessment; HTAi, Health Technology Assessment International; INAHTA, International Network of Agencies for Health Technology Assessment; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; LFN, Pharmaceutical Benefits Board (Sweden); NICE, National Institute for Health and Care Excellence (United Kingdom); NMA, network meta-analysis; NOAC, non-vitamin k antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; PBAC, Pharmaceutical Benefits Advisory Committee (Australia); RCT, randomized controlled trial; RWE, real-world evidence; SE, systemic embolism; VKA, vitamin k antagonist; WTP, willingness-to-pay.

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1. Introduction

1.1. HTA assessments across countries

Health technology assessment (HTA) is a systematic evaluation of treatments to inform health policy, access and reimbursement decision-making [1]. There are more than 40 countries with HTA agencies generating HTA recommendation reports in their respective markets [2,3]. Different HTA archetypes exist across countries; these are defined by the focus of their assessment (i.e., clinical and/or economic evidence), methods employed, submission processes and requirements, payment/reimbursement systems, national or regional assessments, and other pricing and pharmacoeconomic factors [4]. Prior research found that differences in assessment methodologies, mandates and political systems across countries can lead to variations in final recommendations for new drugs [5,6]. To this end, there has been a recent emphasis on a need for more standardized practices in HTA [6,7].

1.2. NOACs for treatment in NVAF

Global assessment is needed for treatments that are approved worldwide to shed insight on potential variation across countries in evaluation and approval of the same treatments. This is particularly pertinent for non-vitamin K antagonist oral anticoagulants (NOACs), specifically apixaban, dabigatran, edoxaban, and rivaroxaban, as they are increasingly being approved and recommended worldwide as treatment for stroke prevention in patients with NVAF [8]. Randomized controlled trials (RCTs) demonstrated that NOACs have similar or better efficacy and safety in comparison to vitamin k antagonists (VKAs) [9–12]. Differently from warfarin, NOACs can be administered without routine monitoring of anticoagulant levels. Despite the clinical advantages of NOACs, warfarin is still widely used in clinical practice, likely due to its established familiarity and lower cost [13].

Although clinical efficacy and cost-effectiveness of NOACs have been assessed [14], no comprehensive review of HTA reports assessing different NOACs exists. Most NOACs have been in the market for several years, while edoxaban was authorized more recently. Some differences in HTA submission methods may have occurred over this broad time horizon, resulting in different recommendations. Assessing the timing of NOAC submissions may reveal whether factors such as patient voices, real-world evidence (RWE), and data from more mature RCTs had an impact in later submissions compared to earlier ones.

1.3. Objective and research questions

To advance this research, we performed a review of global HTAs that evaluated NOACs for treatment of patients with NVAF. We aimed to evaluate similarities and differences across country-level HTAs in methodology, data considerations, final decisions on recommended use of each NOAC, and preferential statements for the NOACs (e.g., related to subgroups, dose, and clinical outcomes). This review addresses two research questions:

1. What was the global clinical and economic value of the NOACs across national HTAs, and what methods, perspectives, and evidence were considered in the evaluation of such value?
2. How closely did HTA decisions and recommendations match the approved regulatory label and results of economic evaluations? If the decisions did not match the approved regulatory label, what factors led to the decisions?

2. Methods

2.1. Data sources, searches, and identification of studies

The search methods used to identify eligible HTA reports consisted of two phases. In phase 1, the websites of INAHTA, HTAi vortal, ISPOR, and the European Network for Health Technology Assessment were searched in August–September 2018 to identify countries and agencies that produce HTA reports (Supplemental Table 1). In phase 2, websites of each HTA agency identified were searched for publicly available HTA documents related to NOACs for prevention of stroke in patients with NVAF (Table 1), using keywords "atrial fibrillation," "oral anticoagulants," "apixaban," "dabigatran," "edoxaban," "rivaroxaban." No geographic, language, or temporal limits were applied to the search.

Documents eligible for inclusion were HTA reports of NOACs for treatment of patients with NVAF. Two investigators independently reviewed the identified documents to determine their eligibility for inclusion in the review. Any discrepancies were resolved by a third independent investigator. Published HTA reports for a given country that evaluated only dabigatran or rivaroxaban were excluded unless such reports evaluating apixaban and edoxaban were also available for the same country; this ensured that the comparison of the four NOACs was similar across countries that evaluated multiple NOACs.

2.2. Data extraction and synthesis

One investigator independently extracted key information from the reports and a second investigator validated data for accuracy. Discrepancies between investigators were resolved by a third, independent investigator. If multiple reports were identified for a single HTA submission, they were extracted as a single report. In cases where updates to HTA reports were available, the more recent applicable evidence took precedence over older documents when summarizing main conclusions. However, all documents were considered in the evaluation of the methodology, results, and conclusions of the HTA reports. Extracted data elements are summarized in Supplemental Table 2. Due to the absence of a standard quality assessment instrument for HTA reports, no formal quality assessment was undertaken in this review.

A qualitative synthesis was performed to summarize key findings and patterns across HTA reports and identify gaps. The synthesis was conducted following an a priori framework with information clustered by country, HTA agency, type of NOAC, and type of evidence (clinical and/or economic) presented in the reports (Supplemental Fig. 1). Addressing the first research question involved synthesis of clinical evidence, including the methods, results and conclusions of RCTs, network meta-analyses (NMAs), and RWE. Additionally, economic evidence, including the methods, results and conclusions of economic evaluations, were synthesized. The cost-effectiveness results and willingness-to-pay (WTP) thresholds were converted to 2019 Euros for comparability. The cost conversions were completed by first inflating values to the year 2019 and then using country-specific conversion rates to convert each currency to Euro [15–20]. In answering the second research question, the final recommendations of the assessments, drivers of decisions, and approved regulatory labels reported in each HTA report were collated and compared. In addition, comments from patients and patient representatives considered in HTAs were categorized and compared.

3. Results

3.1. Search results

Phase 1 searches yielded websites for 68 agencies across 36 countries (Supplemental Table 1). The phase 2 search of agency websites yielded 8886 records. Results by country appear in Supplemental Table 3. Fifty HTA reports (38 unique and 12 related documents) from 16 countries were included in this review (Supplemental Fig. 2). Despite no date limit set on the search strategy, the publication date of included reports ranged from 2012 to 2017. This aligns with the approval date of NOACs (2011–2015). Among the reports, four were from Netherlands, four Sweden, two Colombia, two Poland, one Spain and one Brazil.

Table 1
HTA characteristics by country (n = 16).

Country, year[a] (# of reports)	Agency	A	D	E	R	VKA	ASA	Clinical evidence	Economic evidence	Patient input
Australia, 2013 (7)	PBAC	✓	✓		✓	✓	✓	RCT, NMA of RCTs, RWE	CEA, CUA, CMA	No
Belgium, 2017 (1)	KCE	✓	✓	✓	✓	✓		NMA of RCTs	SLR of CEAs	No
Brazil, 2016 (1)	CONITEC	✓	✓		✓	✓		RCT, NMA of RCTs	Cost comparison	Yes
Canada, 2013[b] (5)	CADTH	✓	✓	✓	✓	✓	✓	RCT, NMA of RCTs	CUA	Yes
Colombia, 2016 (2)	IETS	✓	✓		✓	✓		RCT, NMA of RCTs	CEA	No
England, 2017 (5)	NICE	✓	✓	✓	✓	✓	✓	RCT, NMA of RCTs, RWE	CEA, CUA	Yes
France, 2016 (1)	HAS	✓	✓	✓	✓	✓		RCT, NMA of RCTs	NA	No
Germany, 2013 (1)	IQWiG	✓				✓	✓	RCT	NA	No
Ireland, 2013 (3)	NCPE	✓	✓		✓	✓	✓	RCT, NMA of RCTs	CEA	No
Netherlands, 2015 (4)	GVS, CVZ, CFH	✓	✓	✓	✓	✓		RCT	CUA	No
Norway, 2013 (1)	NoMA	✓	✓		✓	✓		RCT, NMA of RCTs, other HTAs	CUA	No
Poland, 2013 (2)	AOTMiT	✓	✓	✓	✓	✓	✓	RCT, NMA of RCTs	CUA	No
Scotland, 2015 (4)	SMC	✓	✓	✓	✓	✓	✓	RCT, NMA of RCTs	CUA	Yes
Singapore, 2018 (1)	ACE	✓	✓		✓	✓		RCT	CEA, CMA	No
Spain, 2016 (1)	AEMPS	✓	✓	✓	✓	✓		RCT	NA	No
Sweden, 2016 (4)	TLV	✓	✓	✓	✓	✓		RCT, NMA of RCTs, RWE	CEA, CMA	No

Abbreviations: A = apixaban; ACE = Agency for Care Effectiveness; AEMPS = Agencia Española de Medicamentos y Productos Sanitarios; AOTMiT = Agency for the Assessment of Medical Technology and Tariffs; ASA = aspirin; CADTH = Canadian Agency for Drugs and Technologies in Health; CEA = cost-effectiveness analysis; CFH = Committee of Pharmaceutical Aid; CMA = cost-minimization analysis; CONITEC = National Committee for Technology Incorporation; CUA = cost-utility analysis; CVZ = Health Care Insurance Board; D = dabigatran; E = edoxaban; GVS = Medicine Reimbursement System; HAS = Haute Autorité de Santé; IETS = Institute of Technological Evaluation in Health; IQWiG = Institute for Quality and Efficiency in Health Care; KCE = Belgian Health Care Knowledge Centre; NA = not applicable; NCPE = National Centre for Pharmacoeconomics; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NoMA = Norwegian Medicines Agency; PABC = Pharmaceutical Benefits Advisory Committee; R = rivaroxaban; RCT = randomized controlled trial; RWE = real-world evidence; SLR = systematic literature review; SMC = Scottish Medicines Consortium; TLV = Dental and Pharmaceutical Benefits Agency; VKA = vitamin K antagonist.

[a] When more than one report was published for a given country, the characteristics were combined, and the most recent date was reported.

[b] All reports in 2013, except edoxaban report in 2017.

3.2. HTA report characteristics

Among the 16 countries with HTA reports providing clinical and/or economic results for NOACs, all (100%) reported on apixaban, 15 (94%) on dabigatran and rivaroxaban, and 10 (63%) on edoxaban. Publication years ranged from 2011 to 2018, with 52% published in 2012 and 2013. All HTA reports included evidence on stroke and major bleeding, and all but one reported evidence for systemic embolism (SE) [21,22]. Eleven of 16 (69%) countries were European; the remaining countries were Canada, Brazil, Colombia, Australia, and Singapore. Thirteen (81%) countries provided both clinical and cost-effectiveness results (in one or across multiple reports); HTA documents for Germany, France, and Spain reported only clinical results. Reports from only four countries (25%) considered patient voice [23–33]. The characteristics of included HTA reports by country are summarized in Table 1.

3.3. Clinical and economic value (research question 1)

3.3.1. Clinical evidence

All 38 HTAs reported clinical evidence, from either RCTs (n = 38), NMAs of RCTs (n = 26), or RWE (n = 8; Table 1). None of the RCTs compared two or more NOACs directly. Hence, HTA agencies compared two NOACs using RCTs comparing NOACs with vitamin K antagonists or aspirin in an NMA.

Among the 26 HTAs presenting NMA results, six (26%) reported one NOAC's clinical superiority over another [21,25,34–37]. For primary outcomes (stroke, SE, and/or major bleeding), apixaban had significantly better clinical efficacy and safety compared with dabigatran (n = 4), rivaroxaban (n = 2), and edoxaban (n = 1), and dabigatran had significantly better efficacy and safety than rivaroxaban. Edoxaban had significantly lower major bleeding risk compared with dabigatran (n = 1) and rivaroxaban (n = 2). No HTA reports showed rivaroxaban to be clinically superior to another NOAC.

RWE was sparsely considered in HTA reports. Two reports included RWE in the clinical inputs, but there was no evidence suggesting the additional RWE impacted the main conclusions of the reports [38,39].

3.3.2. Economic evidence

Among the 35 reports examining NOACs' cost-effectiveness, the most commonly used methods were cost-utility analysis (CUA) (n = 18) and cost-effectiveness analysis (CEA) (n = 19), alone or in conjunction with other methods (Table 2). Among these, all reported QALY estimates and four of the CUAs (Canada, Norway, and Scotland) reported QALYs and cost per life-year [30,40–42]. Cost per life-year was also reported by two reports that used both CEA and CUA from the Netherlands [43,44]. Four reports presented information from cost-minimization analyses (CMAs) (Australia [n = 2], Singapore, and Sweden). CEA and CMA were both presented in reports from Australia and Singapore [45–48]. Eleven HTAs (six countries) reported WTP thresholds; a drug that was not cost-effective based on these thresholds was not recommended by the country's agency. The WTP was comparable across countries and agencies. The thresholds ranged from 20,000 to 50,000 in United States dollars, British pounds, or Euros (Table 2). When converted to Euros, the range was still 20,000 to 50,000 with the exception of one report from Norway that gave a WTP threshold of 580,000 Norwegian krone (€68,963) [41]. Of note, the review included four reports from the Netherlands, two assessing clinical and economic value (dabigatran and rivaroxaban) [43,44] and two reporting clinical value only (apixaban and edoxaban) [36,49]. The clinical value only reports (Germany [50], France [35], and the Netherlands [apixaban and edoxaban]) were not considered for economic value or final recommendations.

3.3.3. Budget impact models

Thirty-five reports presented economic evidence, 13 of which included a budget impact model (BIM) (see Supplemental Table 3) [21,23,28–30,34,37,41,42,47,51–53]. Australia and Ireland were the only countries with reports comparing NOACs directly in the BIMs. The remaining countries compared NOACs with warfarin and/or aspirin.

3.3.4. HTA recommendations

3.3.4.1. NOACs vs. warfarin. Most NOACs were considered cost-effective compared with VKAs, based on findings from 14 countries. Of the countries that evaluated cost-effectiveness, most found rivaroxaban (10/13),

Table 2
Characteristics, methods, and economic results of HTA reports.

Country, year	Analysis time horizon	WTP	Comparison	Summary metric	Summary metric in 2019 Euros	Preferential statement
Australia, 2013	CEA and CMA 10–20 years	NR	A, D, R vs. warfarin A vs. D, R	A$45,000–75,000/QALY NR	€32,395-53,991/QALY[a] NA	Committee agreed to substitution of warfarin, aspirin, and potentially from no treatment with NOACs.
Australia, 2011	CEA Lifetime	NR	D vs. warfarin	A$15,000–45,000/QALY	€10,798-32,395/QALY[a]	Dabigatran 150 and 110 mg recommended based on acceptable cost-effectiveness
Australia, 2013	CUA NR	NR	R vs. warfarin	A$15,000–45,000/QALY	€10,357-31,072/QALY[a]	Rivaroxaban recommended based on cost-effectiveness compared with warfarin.
Belgium, 2017	SLR of CEAs NR	NA	NOACs vs. VKAs	NA		NOACs were considered cost-effective against VKAs
Brazil, 2016	Cost comparison NA	NA	A, D, R vs. warfarin	NR		The committee concluded that a disadvantage of NOACs are its higher costs.
Canada, 2013	CUA 30–40 years (lifetime)	NR	A vs. warfarin D 150 vs. warfarin D 110 vs. warfarin R vs. warfarin A vs. D A vs. R A, D, R vs. warfarin	C$24,312/QALY C$17,525/QALY C$96,026/QALY C$55,757/QALY NR NR NR	€17,542/QALY[b] €12,645/QALY[b] €69,287/QALY[b] €40,231/QALY[b] NA NA NA	The committee concluded that the relative cost-effectiveness of the NOACs is uncertain.
Canada, 2017	CUA Lifetime	NR	E vs. warfarin E vs. R	C$12,672/QALY NR	€8702/QALY[b]	Edoxaban was cost-effective compared with warfarin. Dominated
Colombia, 2016	CEA Lifetime	NR	A vs. warfarin D 150 vs. warfarin R vs. warfarin D vs. R D vs. A	COL$97,501,541/QALY COL$74,462,000/QALY COL$91,981,682/QALY NR NR	€29,600/QALY[c,d] €22,605/QALY[c,d] €27,924/QALY[c,d] NA NA	The committee concluded that costs of the NOACs were three times Colombia's GDP per capita.
England, 2015	CEA 30 years	NR	D 150 vs warfarin A vs. warfarin E vs. warfarin D 110 vs. warfarin R vs. warfarin	£7645/QALY £9383/QALY £12,881/QALY £13,565/QALY £28,180/QALY	€9516/QALY[e] €11,679/QALY[e] €16,033/QALY[e] €16,884/QALY[e] €35,075/QALY[e]	The NOACs strictly dominated over warfarin, but evidence is insufficient for cost-effectiveness among the NOACs.
England, 2017	CEA Lifetime	£20,000/QALY	NOACs vs. warfarin	NR	NA	Use of NOACs may be cost-effective compared with warfarin.
England, 2012	CUA Lifetime CEA Lifetime	£20,000; £30,000 (€26,710; €40,065) £20,000; £30,000 (€26,710; €40,065)	D vs. warfarin R vs. warfarin D vs. warfarin R vs. D	£18,900/QALY £18,883/QALY £34,680 NR	€25,241/QALY[e] €25,218/QALY[e] €46,315/QALY[e] NA	Dabigatran was cost-effective compared with warfarin. Rivaroxaban was more cost-effective than dabigatran and warfarin
France, 2016	NA	NA	NA	NA	NA	NA
Germany, 2013	NA	NA	NA	NA	NA	NA
Ireland, 2013	CEA NR	€45,000/QALY (€45,967/QALY)	A vs. warfarin A vs. D A vs. R	€23,669/QALY NR NR	€24,177/QALY[e]	Apixaban was cost-effective compared with dabigatran, rivaroxaban, and warfarin.
Ireland, 2012	CEA 30 years	€20,000–30,000/QALY	R vs. warfarin	€22,663/QALY	€23,219/QALY[e]	Rivaroxaban is not cost-effective compared with warfarin.
Ireland, 2011	CEA NR	€20,000–30,000/QALY	D vs. warfarin	<80 years: €6311/QALY 80 years or older: €20,654/QALY	<80 years: €6492/QALY[e] 80 years or older: €21,246/QALY[e]	Dabigatran may be cost-effective compared with warfarin in patients with risk factors, but models contain uncertainties.
Netherlands, 2012	CUA Lifetime	NR €20,000/QALY NR	D vs. warfarin R vs. warfarin D vs. R	€7719 €11,396/QALY NR	€8275 €12,217/QALY[e] NA	Dabigatran is cost-effective compared with warfarin. Rivaroxaban is cost-effective compared with warfarin. Dabigatran is interchangeable with rivaroxaban.

Table 2 (*continued*)

Country, year	Analysis time horizon	WTP	Comparison	Summary metric	Summary metric in 2019 Euros	Preferential statement
Norway, 2013	CUA Lifetime	NOK 588,000/QALY (€68,963)	R vs. warfarin	CHADS2-VASc = 1 and HAS-BLED = 0: NOK 317,550/QALY CHADS2-VASc = 2 and HAS-BLED = 1: NR	€37,243/QALY[f]	All NOACs were cost-effective compared with warfarin for patients of medium to high risk of stroke. Dabigatran 150 mg was the most cost-effective.
			D 150 vs. warfarin	CHADS2-VASc = 1 and HAS-BLED = 0: NOK 328,174/QALY CHADS2-VASc = 2 and HAS-BLED = 1: NOK 106,142/QALY	CHADS2-VASc = 1 and HAS-BLED = 0: €38,489/QALY[f] CHADS2-VASc = 2 and HAS-BLED = 1: €12,449/QALY[f]	
			A vs. warfarin	CHADS2-VASc = 1 and HAS-BLED = 0: NOK 881,627/QALY CHADS2-VASc = 2 and HAS-BLED = 1: NR	CHADS2-VASc = 1 and HAS-BLED = 0: €103,400/QALY[f] CHADS2-VASc = 2 and HAS-BLED = 1: NA	
			A vs. D	CHADS2-VASc = 1 and HAS-BLED = 0: NOK 882,000/QALY CHADS2-VASc = 2 and HAS-BLED = 1: NR	CHADS2-VASc = 1 and HAS-BLED = 0: €103,444/QALY[f] CHADS2-VASc = 2 and HAS-BLED = 1: NA	
Poland, 2014	CUA NR	NR	D vs. warfarin	NR	NA	NR
			D vs. A, R	NR	NA	NR
Poland, 2013	CUA Lifetime	NR	A vs. warfarin	NR	NA	NR
			A vs. aspirin	NR	NA	NR
Scotland, 2013	CUA Lifetime	NR	A vs. warfarin	£12,119/QALY	€15,795/QALY[e]	Apixaban was cost-effective compared with warfarin and dabigatran.
			A vs. D	£13,467/QALY	€17,552/QALY[e]	
			A vs. R	NR	NA	Dominated
Scotland, 2015	CUA 30 years	NR	E vs. warfarin	£23,539/QALY	€29,299/QALY[e]	Edoxaban dominated rivaroxaban and was as effective and less costly than apixaban.
			E vs. R	NR	NA	
			E vs. D	NR	NA	
			E vs. A	NR	NA	
Scotland, 2011	CUA Lifetime	£20,000–30,000/QALY (€26,067–39,100/QALY)	D vs. warfarin	£6986/QALY	€9608/QALY[e]	Dabigatran was more cost-effective than warfarin.
Scotland, 2012	CUA Lifetime	£30,000/QALY (€39,100/QALY)	R vs. warfarin	NR	NA	Dominated
Singapore, 2018	CEA and CMA Lifetime	NR	A, D, R vs. warfarin	<$15,000/QALY	NA	NOACs were a cost-effective treatment option compared with warfarin for stroke prevention.
Spain, 2016	NA	NA	NA	NA	NA	NA
Sweden, 2013	CEA NR	NR	Apixaban vs. warfarin	NR	NA	Apixaban and rivaroxaban were cost-effective compared with warfarin.
			Apixaban vs. D, R	NR	NA	
Sweden, 2016	CMA NR	NR	E vs. warfarin	NR	NA	None of the NOACs could be considered superior to others.
			E vs. A, D, R	NR	NA	

Abbreviations: A = apixaban; CEA = cost-effectiveness analysis; CMA = cost-minimization analysis; CUA = cost-utility analysis; D = dabigatran; E = edoxaban; HTA = health technology assessment; NA = not applicable; NOAC = non-vitamin K antagonist oral anticoagulant; NOK = Norwegian Krone; NR = not reported; QALY = quality-adjusted life year; R = rivaroxaban; VKA = vitamin K antagonist; WTP = willingness to pay.

[a] Inflation rate at https://www.rba.gov.au/inflation/measures-cpi.html [15].
[b] Inflation rate at https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1810000401 [16].
[c] Inflation rate at https://www.banrep.gov.co/en/consumer-price-index [17].
[d] Exchange rate at https://www.exchangerates.org.uk/EUR-COP-spot-exchange-rates-history-2019.html [18].
[e] Inflation rate at https://ec.europa.eu/eurostat/web/hicp [19].
[f] Inflation rate at https://www.ssb.no/en/kpi [20].

apixaban (8/12), dabigatran (8/13), and edoxaban (5/7) to be cost-effective over VKAs (Table 3).

3.3.4.2. NOACs vs. other NOACs. Four of 12 countries providing recommendations for apixaban (Canada, Ireland, Norway, and Scotland) reported cost-effectiveness comparisons between apixaban and other NOACs. Rivaroxaban was least cost-effective, as only two countries showed rivaroxaban to be as cost-effective as another NOAC (dabigatran) but was not as cost-effective as apixaban or edoxaban (Table 3). Apixaban, dabigatran and edoxaban were each as or more cost-effective than other NOACs in 2–3 countries (Table 3).

3.3.5. Assessment of HTA methods and approved regulatory label alignment (research question 2) patient voice

Eleven HTA reports across four countries considered the patient voice as part of their assessment (Canada [n = 3 (27%)], Scotland [n = 3 (27%)], England [n = 4 (36%)], Brazil [n = 1 (9%)]) [23–33]. The comments from patients and patient representatives were qualitatively synthesized. Specific inconveniences associated with warfarin included frequency of INR monitoring appointments, which affect day-to-day life and result in lost work time, and the concerns of food-drug, food-alcohol, and drug-drug interactions, which limit social activities and quality of life. Five HTA reports noted that patients or patient

representatives expected that NOAC(s) evaluated would improve quality of life and/or provide relief from the burden of warfarin. Two of the nine HTAs specifically stated that patient data were considered in reaching the final decision about treatment.

3.3.6. Patient access

3.3.6.1. Alignment with approved regulatory label. Of the 38 HTA reports, 14 did not report information on approved regulatory labels. Scotland was the only country that reported the date of the approved regulatory label. To address this missing information, individual agency sources were searched. A summary of the alignments between HTA recommendations and approved regulatory labels appears in Table 4.

Twenty-six of 30 reports with a positive NOAC recommendation aligned with the approved regulatory label, while four did not. In these cases, the HTA report recommended the NOAC for higher-risk group individuals based on $CHADS_2$ score cutoff, but the labels did not reflect that limitation. In two Canadian HTA reports, the recommendation applied to patients with $CHADS_2$ score ≥1, while the regulatory label specified patients with a $CHADS_2$ score ≥2 [40]. In one report from France (clinical only) [35], edoxaban was recommended as a secondary treatment in patients with contraindication, low tolerance, or inability to achieve INR targets with VKAs. In contrast, the approved regulatory label included a broader population of patients with NVAF. A report from Poland recommended dabigatran for a narrower NVAF patient population ($CHADS_2$ score ≥3 and patient ages ≥75) compared to the approved regulatory label was wider [54].

3.3.7. Changes to HTA recommendations over time

Recommendation reports from five countries (Australia, Colombia, Canada, England, and Sweden) were updated or included an addendum. The drivers of such changes were additional sensitivity analyses and variable adjustments and/or additional evidence that were not available at the time of original publication. Three reports (Australia, Canada, England) included more recent published reports to be more inclusive of the NOACs based on market availability In England, the original report (2012) concluded that rivaroxaban was cost-effective versus warfarin [55], whereas the updated documents (2015–2017) with evaluations of all four NOACs, determined that evidence was insufficient to justify conclusions of superiority among the NOACs [25–27]. Similarly, for Canada, one HTA report (2013) did not include apixaban, but the updated report (2017) included data from all four NOACs [24]. The update recommended NOACs over warfarin in patients with a $CHADS_2$ score ≥1 and concluded there was insufficient evidence to decide superiority among the NOACs. In Australia, Colombia, and Sweden, the addenda were driven by requests to evaluate additional variables and perform supplementary analyses to the original report(s) but the additions did not alter the recommendations of each report.

3.3.8. Decision drivers

Decision drivers were usually not explicitly stated in the HTA reports, rather most countries included reasons or rationales for the decisions (Table 4). Sixteen reports concluded that cost-effectiveness was the reason for positive recommendations: three each from Australia [45,46,51] and Canada [56,57]; two each from England [55,58], the Netherlands [43], Norway [41], Scotland [30,42], and Sweden [38,59]. NICE CEA results specifically stated the drivers, which included discontinuation rates on the first line of treatment (apixaban) [25], lower rates of myocardial infarction, intracranial hemorrhage, and other clinically relevant bleeding (apixaban), and hemorrhagic stroke (edoxaban) [26]. Reports from Singapore and Columbia (apixaban, dabigatran, and rivaroxaban only) reported the reason for the reject decisions was the high cost of the NOACs [21,22,47]. Drivers or reasons for decisions were not reported or not publicly available in 13 reports [28,29,34,36,39,45,48,49,52–54,60,61].

4. Discussion

This global review on NOACs for patients with NVAF yielded 38 unique HTA reports (50 documents; 16 countries). Most HTA reports recommended NOACs; few countries recommended one NOAC over another. This can be attributed to the clinical evidence, which was based on indirect comparisons between NOACs (mainly via warfarin) due to the lack of RCTs directly comparing individual NOACs. Cost-effectiveness was a major driver of positive recommendations; if a drug was not cost-effective based on local WTP thresholds, it was not recommended by the respective HTA agency.

Generally, NOACs were recommended by most agencies/countries. Exceptions included Colombia and Brazil, where apixaban, dabigatran, and rivaroxaban were not recommended, mainly due to high drug costs [22,23]. Brazil's HTA agency was concerned with uncertainty around existing trial data and lack of patient monitoring (absence of INR monitoring). Similarly, Singapore did not recommend dabigatran, based on unacceptable cost-effectiveness and budget impact results [47]. In contrast, the high cost of NOACs did not negatively impact results in Canada, Scotland, or England, where all NOACs were recommended over warfarin.

Healthcare cost, quality, and affordability/access could represent potential drivers of HTA decisions across countries and determine drug value. A systematic analysis from the Global Burden of Disease Study in 2016 evaluated healthcare access and quality globally by calculating a Healthcare Access and Quality Index (HAQI) [62]. The HAQI scores range from 0 to 100, with 100 representing the highest-quality healthcare. All countries in the review had high HAQI scores (>90) except for Poland, Colombia, and Brazil. Colombia and Brazil are two of the countries in our review that did not recommend NOACs (HAQI scores of 62 and 64, respectively).

Canada, Scotland, and England were the only countries whose reports considered the patient voice; however, only one report from England incorporated such data into the final decision [23–33]. The few reports in this review that considered patient voice concluded there was an inconvenience and burden associated with warfarin that was not considered in the RCTs evaluating clinical efficacy and safety.

RWE was also sparsely considered in the HTA reports or updates. Three countries (Sweden, Australia, and Spain) mentioned the RELY-ABLE study, an observational follow-up of the RE-LY trial [63]. Sweden was the only country with reports including additional RWE in the clinical evidence. A potential reason for the lack of RWE in the NOAC HTAs is the year of publication. A limited number of HTA reports ($n = 11$) were published in 2016 or later. Recent systematic literature reviews of RWE in NOACs have identified an absence of comparative RWE among the NOACs, particularly prior to 2015 [64,65]. Additionally, the use of RWE in HTAs is inconsistent highlighting a need for a policy on RWE [66]. Only in the last few years has the inclusion of RWE in HTAs gained traction.

Each HTA agency has a different drug-implementation program, with varying systems, regulations, and drug-approval processes related to patient access. One of the objectives of this review was to gain insights into global variations in patient access and implementation of HTA recommendations. However, information on these topics was rarely included in the HTA reports.

When evaluating discordance between HTA agency recommendations, it is useful to understand commonalities and differences between HTA agencies. For example, HTA agencies for Canada, Scotland, and England have much in common regarding how they evaluate new treatments and value the opportunity for early engagement with companies targeting their markets—NICE and CADTH recently launched a new collaboration to offer parallel scientific advice to the life sciences industry [67]. Hence, it is not surprising that these agencies would align in their NOAC recommendations. In contrast, as highlighted by a case study of HTA systems in Australia, Canada, England and Scotland, these four countries provided divergent recommendations using similar rationale and information [6]. The variation in consideration of varying factors,

Table 3
Summary of cost-effectiveness and recommendations across NOAC vs. NOAC and NOAC vs. VKA comparisons by country.

Intervention	Number of countries with positive recommendations	Countries where the intervention demonstrated economic value vs. the following treatments:				
		VKA	Apixaban	Dabigatran	Edoxaban	Rivaroxaban
Apixaban	Overall: 10/12[a] vs. VKAs: 8/12[a] vs. NOACs: 3/5[a]	8: Australia, Belgium, Canada, Ireland, Norway, Singapore, Sweden, England	NR	2: Ireland, Scotland	1: Canada	3: Canada, Ireland, Scotland
Dabigatran	Overall: 10/13 vs. VKAs: 8/13 vs. NOACs: 3/9	8: Australia, Belgium, Canada, Ireland, Netherlands, Norway, Singapore, England	1: Norway	NR	0	3: Norway, Australia, Sweden
Edoxaban	Overall: 5/7 vs. VKAs: 5/7 vs. NOACs: 2/5	5: Belgium, Canada, Scotland, England, Sweden	0	0	NR	2: Canada, Scotland
Rivaroxaban	Overall: 10/13 vs. VKAs: 10/13 vs. NOACs: 2/8	10: Australia, Belgium, Canada, Ireland, Netherlands, Norway, Scotland, Singapore, Sweden, England	0	2: England, Netherlands	0	NR

Abbreviations: NOAC = non-vitamin K antagonist oral anticoagulant; NR = not reported; VKA = vitamin K antagonist.
[a] The HTA on apixaban from the Netherlands did not report economic results and was not included in the denominator.

during the decision-making and recommendation process by the agency could be a driver of conflicting conclusions based on similar evidence [6]. In the present review, similar evidence for clinical efficacy and safety of the NOACs was used across the HTA reports, but a few countries did not recommend the use of the NOACs. The differences in scientific standards, country-specific considerations, and variation in agency consideration could be a factor in some of the differences seen in the recommendations across agencies.

Finally, this review has several limitations. The search covered a wide range of global HTA bodies with no language limits. For search and screening, when available, native speakers were utilized to search for non-English reports on agency websites, as the websites need to be searched manually and cannot be searched with search strings like electronic databases. However, if a native language speaker was not available, searchers and reviewers relied on translation tools, which are not always accurate and may have caused some reports to be missed. However, if any potentially relevant reports were identified by automated translation tools during screening, they were included for full translation. Another limitation was that information in HTA reports did not comprehensively address the research questions related to patient access. For example, many reports did not state dates of approved regulatory labels, so dates were collected from agency websites. Judgment calls were made on whether the recommendations matched the approved regulatory label. An additional limitation of this review is that data collection was based on public availability of information, which varies by country and agency. Countries like England, Australia, and Canada have a plethora of documents supporting HTA reports online with final decisions. In contrast, some countries, such as Poland, concealed methodological details and results from the publicly available version, limiting our access to comprehensive data.

5. Conclusions

The present review furthered the existing research in assessing HTA methods and variation in HTAs across countries worldwide. Through the evaluation of HTA reports on NOACs for the treatment of NVAF, we observed differences in methods and processes, such as methodology, patient involvement and included NOACs. However, only a portion of the differences across HTAs can be evaluated based on the report information. Other factors and data sources should be taken into account

Table 4
Patient access information: approval dates, HTA publication date, and match of recommendation to approved regulatory label.

Country	Apixaban		Dabigatran		Rivaroxaban		Edoxaban		Match	Key drivers or conditions
	Approval	HTA Pub	Approval	HTA Pub	Approval	HTA Pub	Approval	HTA Pub		
Australia	Jul 2011	Mar 2013[a]	May 2011	Mar 2013[a]	May 2012	Mar 2013[a]	NA	NR	Yes	Cost
Colombia	Jul 2012	May 2016[c]	Feb 2011	Dec 2014[c]	Feb 2012	May 2016[c]	NA	NR	No	Rejected - cost
Netherlands	Sept 2012	Feb 2013[b]	Aug 2013	Jun 2012[a]	Jun 2012	Oct 2012[a]	Feb 2015	Sept 2015[b]	Yes	Clinical efficacy and safety
Germany	Nov 2012	Jan 2017[a]	Aug 2011	Jan 2017[a]	Dec 2011	Jan 2017[a]	Jun 2015	Jan 2017[a]	NA	Clinical only
England	Nov 2012	Mar 2017[a]	Aug 2011	Mar 2012[a]	Dec 2011	May 2012[a]	Jun 2015	Nov 2017[a]	Yes	Clinical data and cost of INR monitoring
Belgium	Nov 2012	Mar 2013[b]	NA	NR	NA	NR	NA	NR	Yes	Clinical efficacy and safety
Ireland	Nov 2012	May 2013[a]	Aug 2011	Aug 2011[a]	Dec 2011	Mar 2012[a]	NA	NR	Yes	NR
Norway	Nov 2012	Mar 2013[a]	Aug 2011	Mar 2013[a]	Dec 2011	Mar 2013[a]	NA	NR	Yes	Assumptions in model
Poland	Nov 2012	Aug 2013[a]	Aug 2011	Jun 2014[a]	NA	NR	NA	NR	No	Price and narrow population (CHADS2 score ≥3 and ≥75 years old)
Scotland	Nov 2012	Jan 2013[a]	Aug 2011	Sept 2011[a]	Dec 2011	Feb 2012[a]	Jun 2015	Oct 2015[a]	Yes	Clinical efficacy and safety
Sweden	Nov 2012	May 2013[a]	Aug 2011	Aug 2016[a]	Dec 2011	Aug 2016[a]	Jun 2015	Jun 2016[a]	Yes	Cost
Spain	Nov 2012	Nov 2016[b]	NA	NR	NA	NR	NA	NR		NR
Canada	Dec 2012	Mar 2013[a]	Oct 2010	Jul 2013[a]	Jan 2012	Jul 2013[a]	Oct 2016	Apr 2017[a]	Yes	Clinical data and cost
Brazil	Jul 2013	Feb 2016	Dec 2011[c]	Feb 2016[c]	Sept 2011	Feb 2016[c]	NA	NR	No	Rejected – Cost
Singapore	Dec 2012	Oct 2018[a]	Mar 2011	Oct 2018[c]	Mar 2012	Oct 2018[a]	NA	NR	No	Rejected – Cost
France	NA	NR	NA	NR	NA	NR	Jun 2015	Jul 2016[b]	No	Clinical only – heterogeneity in trial methods and population

Abbreviations: HTA = health technology assessment; INR = international normalized ratio; NA = not applicable; NR = not reported.
[a] Recommended
[b] No recommendation.
[c] Not recommended.

to gain a systemic understanding, such as agency regulation, healthcare systems, socioeconomic status, and political climate. Given the variation in HTA methodology across countries and the multifactorial influence on drug recommendations, differences in recommendations across various HTA agencies should be assessed considering the above factors and should not be generalized across different countries.

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Author statement

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Declaration of competing interest

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Appendix A. Supplementary data

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